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PULMONARY EXTRAVASCULAR FLUID DYNAMICS IN OXYGEN TOXICITY.(U)
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DUKE UNIVERSITY MEDICAL CENTER

Department of Anesthesiology

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Title: Pulmonary Extravascular Fluid Dynamics in Oxygen Toxicity.

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FINAL TECHNICAL REPORT

Introduction. Pulmonary oxygen toxicity in man is heralded by the onset of symptoms primarily referred to the upper airway (retrosternal discomfort, feelings of chest tightness and coughing on deep inspiration). Much has been made of the dose/response importance of quantified decrements in vital capacity as evidencing parenchymal injury (1), yet such decrements also can be interpreted in terms of airway irritation. Early indications of pulmonary parenchymal injury generally involve manifestations of increased lung water content (2). We have made comparative studies of lung water content (V_{tiss}), pulmonary capillary blood flow (Q_C) and pulmonary diffusing capacity (D_LCO) with vital capacity (V_C) and onset of symptoms during the development of early pulmonary oxygen toxicity in man.

Methods. Fourteen male volunteer subjects aged between 21 and 38 were included in the study. Four subjects were heavy smokers. Each subject underwent a series of measurements performed during air breathing, 100% oxygen breathing over six hours at normal atmospheric pressure (1 ATA); six hours breathing humidified 100% O_2 at 2 ATA; six hours breathing 100% O_2 dry at 2 ATA; and six hours breathing 100% humidified O_2 at 2.25 ATA. In addition, each subject was studied at 24, 48 and 72 hours after each 2 and 2.25 ATA exposure. Studies on individual subjects were spaced so that no effects of any exposure would be cummulative with respect to other exposures. The protocol was approved by the Clinical Investigation Committee and informed consent was obtained. Duplicate measurements of V_{tiss}, Q_C and D_LCO were made using a rebreathing technique with simultaneous gas analysis by quadrupole mass spectrometry (2,3). Vital capacities were obtained by spirometry, using in each case, the best of three measurements. Each battery of studies was repeated at 30 minute intervals throughout each exposure, and at 24, 48 and 72 hours following hyperbaric oxygen exposures.

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Results. No symptoms of pulmonary oxygen toxicity were reported during control exposures, but began to develop from the fourth hour of exposure at 2.0 and 2.25 ATA. In each case, symptoms developed first in the four smokers, being the only subjects to report respiratory discomfort during the 2.0 ATA humidified O_2 exposure. Twelve subjects, including the smokers, developed symptoms during the dry O_2 exposure at 2 ATA, again from the fourth hour on. Six subjects developed symptoms during their 2.25 ATA humidified O_2 exposures. The severity of symptoms progressively increased with the exposure.

Despite careful measurements of V_C, we found no consistent decrement caused by the O_2 exposures. Variability of measurement in each subject was $\pm$ 2%, so that we felt confident of detecting a 5% decrement as predicted from previous work (1).

Only in the final hour of the dry O_2 exposure at 2.0 ATA and that of the humidified O_2 exposure at 2.25 ATA was any increase in V_{tiss} detected. This was seen in the same 4 subjects, 2 of whom were smokers, and was of the order of a 50% increase (673 $\pm$ 248 to 960 $\pm$ 328 ml). No such increase was seen in the remaining subjects. Moreover, in those subjects whose V_{tiss} increased, the increase persisted for at least 24 hours following the exposures, but returned to control values by 48 and 72 hours.

Pulmonary diffusing capacity was diminished in all subjects throughout each hyperbaric oxygen exposure (28 $\pm$ 4 ml/min/mm Hg down to 19.2 $\pm$ 1.5). This was primarily caused by reduced CO uptake by hemoglobin because of the increased number of competing O_2 molecules. However, in those subjects who developed an increase in V_{tiss} in the final hour of the 2 ATA dry O_2 exposure and the humidified O_2 exposure at 2.25 ATA, D_{LCO} was further decreased to 16 $\pm$ 1.2 ml/min/mm Hg. Again, in the same subjects, a reduction in D_{LCO} when compared with control values was seen during the 24 hour post exposure studies, but not at 48 or 72 hours.

Measurements of Q_C showed no consistent differences with respect to controls during or after any of the hyperbaric exposures. Values ranged between 5.6 $\pm$ 1.0 and 8.9 $\pm$ 0.8 L/min.

Discussion. The pathophysiology of early pulmonary oxygen toxicity centers around injury to the Type II pneumocyte with a progressive disruption of surfactant structure, and a concomitant increase in intracellular and interstitial water content. We reasoned that the measurement of V_{tiss} and D_{LCO} during the onset of early pulmonary O_2 toxicity would provide a more insightful, yet non-invasive, indicator of the underlying pathophysiology than a decrement in V_C, since this would be caused by acute airway irritation, as by a reduction in pulmonary compliance, our studies were originally designed to determine the contribution of an early accumulation of lung water to the observed decrement in V_C. Because of previous authoritative reports of a dose/response relationship between hyperbaric oxygen exposure and diminution in vital capacity (1), we were surprised to find no such relationship in our studies.

The rebreathing technique for the determination of V_{tiss} is fraught with great variability, so that quite large increases must be present to be reliably detected. Inherent in the method is the requirement for complete gas mixing within the lung within several rebreathing breaths. Further, the technical problems associated with the technique are compounded by the hyperbaric O_2 environment. Hence, a consistent increase in V_{tiss} in the same subjects over at least 4 separate measurements, persisting at normal atmospheric pressure over at least 2 further measurements 24 hours, and subsequently returning to control values in the following 4 to 6 measurements, indicates that water does indeed accumulate in the lungs of normal man during the earliest stages of pulmonary O_2 toxicity. Symptoms develop well in advance of objectively measureable and reversible pathophysiology, therefore represent the earliest reliable indicator of impending pulmonary O_2 toxicity.

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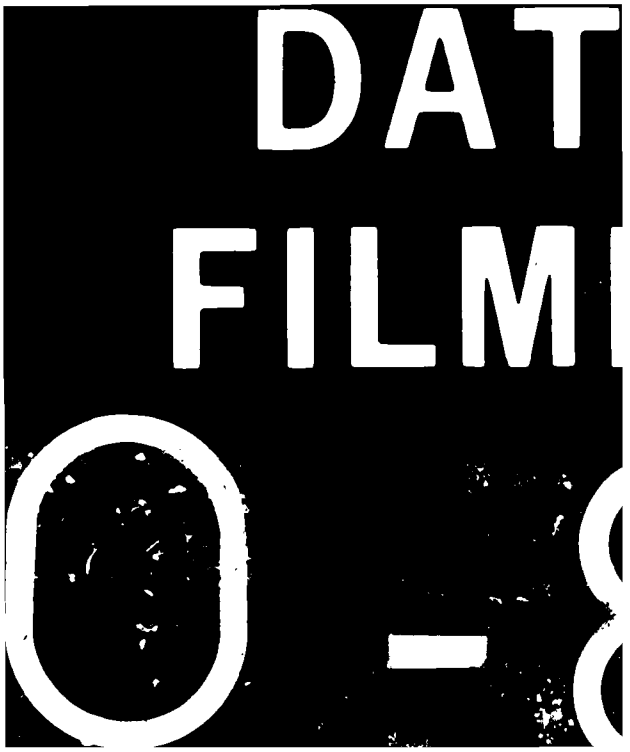
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